The examiner states that the application contains sequence disclosures but fails to comply with the requirements of 37 C.F.R. §1.821-1.825. Appropriate paper copy and computer readable forms of the sequence listing have been required along with the appropriate statements that the paper and computer-readable copies are the same and include no new matter.

Applicants have substituted into the present specification a new paper copy Sequence Listing section according to 37 C.F.R. §1.821(c) as new pages 1-6. Furthermore, attached hereto is a 3 1/2" disk containing the "Sequence Listing" in computer readable form in accordance with 37 C.F.R. §1.821(e).

The following statement is provided to meet the requirements of 37 C.F.R. §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sheets of the sequence listing are believed to be supported in the application as filed and that the substitute sheets of the sequence listing are not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is the same as the attached substitute paper copy of the sequence listing.

Accordingly, all of the sequence listing requirements have now been complied with.

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Claims 1, 10, 22 and 23 have been objected to because of the misspelling of the term "complement" and the recitation in claim 1 of "Type IFN" where "Type I IFN" appears to be intended.

The claims have now been amended to correct the misspellings and make the other correction noted by the examiner, thus obviating this objection.

Claims 10, 11, 15-17 and 21 have been rejected under 35 USC 102(b) as being anticipated by either Cohen or the European patent to Yeda. The examiner states that each of the references describes the preparation of covalently cross-linked complexes of IFNAR2 polypeptides with IFNα species and that the references describe binding affinity experiments in which IFNα molecules are incubated for a time with IFNAR2 receptor molecules. The examiner states that such incubations reasonably appear to meet the limitation of "storing" as required by claim 21. The examiner states that the rejection could be obviated as to the product claims by requiring, for example, that the molecule be capable of effecting the characteristic activities of the Type I IFN component and that method claim 1 would be free of the present rejection if amended, for example, to require the preparation of an article of manufacture comprising a sterile formulation of the IFN-IFNAR complex. This rejection is respectfully traversed.

In both Cohen and Yeda, the IFNAR is covalently bound by cross-linking to ^{125}I-IFN-α2. This radiolabelled interferon is not a native Type I IFN as set forth in claim 10(a), nor is it a fragment of native Type I interferon IFN as set forth in claim 10(b). Furthermore, as it does not differ by a change in the

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amino acid sequence, it is not a variant as set forth in paragraphs (c) or (d) of claim 10. Rather, if anything, it would fall under the definition of "derivative" as it is prepared from the functional groups which occur as side chains on the residues or the N- or C-terminal groups. However, the radiolabelled interferon does not satisfy the definition of "functional derivative" as set forth in the first paragraph on page 30 which specifically defines such derivatives as being "included in the invention as long as they remain pharmaceutically acceptable, i.e., they do not destroy the biological activity of the corresponding protein of the complex as described herein and do not confer toxic properties on compositions containing it or the complex made therefrom." A radio-iodinated interferon complex will confer toxic properties on the composition. Accordingly, it does not fall within the definition of functional derivative as set forth in the specification. Applicant understands that by this statement made herein, applicant will be estopped from arguing in the future that ^{125}I does not confer toxic properties on the complex. Accordingly, a cross-linked complex of IFNAR with radio-labelled interferon does not fall within the scope of a molecule as claimed in claims 10, 11, or 15-17.

With respect to claim 21, the phrase "in a pharmaceutically acceptable formulation" has been added at the end. As the examiner recognizes, neither Cohen nor Yeda disclose the preparation of an article of manufacture comprising a pharmaceutically acceptable formulation of the IFN-IFNAR complex.

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Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 10, 11, 15-17, 21 and 22 have been rejected under 35 USC 102(b) as being anticipated by the Novick (1995) publication. The examiner states that Novick (1995) describes the purification to homogeneity of p40 which is a sIFNAR2 polypeptide, its incubation with IFNα2 under conditions which permit the IFN to bind to the soluble receptor, and the covalent cross-linking of the complex with DSS. For the reasons discussed above with respect to the Cohen and Yeda references, the examiner believes that the cross-linked complexes meet the limitation of the product claims and the incubation meets the broadest reasonable construction of the "storing" step required by claim 21. The examiner further considers that the incubation mixture described by the reference would have been suitable for physiological purposes. The examiner states that the exemplary amendments discussed with respect to the previous rejection would also obviate this ground of rejection. The examiner states that the rejection of claim 22 could be overcome by specifying that the pharmaceutical formulation consists essentially of the recited IFN-IFNAR complex and a carrier. This rejection is respectfully traversed.

The description of Novick (1995) at page 713 to which the examiner refers also relates only to cross-linking of ^{125}I-IFN-α2 to IFNAR. As discussed above, radio-labelled interferon is not a "functional derivative" as this term is used in the claims and defined in the present specification. Accordingly, claims 10, 11

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and 15-17 are free of this reference for the same reasons as discussed above with respect to the Cohen and Yeda references.

With respect to claim 21, the amendment to claim 21 renders claim 21 free of anticipation by Novick (1995) for the reasons suggested by the examiner. As to claim 22, the preamble has been amended to specify that the pharmaceutical composition is one "consisting essentially of" a pharmaceutically acceptable carrier and an IFN-IFNAR complex. As the examiner recognizes, this language excludes the additional components of Novick (1995) and thus obviates the anticipation rejection. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claim 1-3 and 7-9 have been rejected under 35 USC 103(a) as being unpatentable over the U.S. patent to Novick (Novick '078) or the European patent to Yeda. The examiner states that all of claims 1-3 and 7-9 read on methods in which exogenous IFN and IFNAR components are administered separately to a patient whereby a complex is presumed to form *in vivo*. Although the claims require that the amounts administered be sufficient to provide interferon therapy, the examiner states that the references teach that type I interferons are known in the art as therapeutic agents for the treatment of various diseases and that where the levels of such exogenously administered interferon become undesirably high, soluble IFN-α/β receptor may be advantageously administered to modulate the excess IFN. Thus, the examiner considers it to have been obvious to administer a high level of IFN to a patient for a disease known in the art to be responsive to such treatment, to monitor the level of IFN activity in the patient, and to

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subsequently administer a soluble IFNAR2 polypeptide to the patient to modulate an undesirably high level of IFN. The examiner states that such therapy would necessarily meet the limitation of employing amounts of IFN and sIFNAR "effective to provide [interferon] therapy." The examiner states that this ground of rejection would be obviated, for example, by adding a limitation requiring that the IFN and IFNAR agents be employed in amounts such that the therapeutic efficacy of the IFN is potentiated relative to that which would be obtained with the same amount of IFN in the absence of the IFNAR.

In order to obviate this rejection, claim 1 has now been amended to insert at the end the proviso that when the Type I IFN and the IFNAR are administered separately and the complex is formed *in vivo*, the amount of IFNAR administered is an amount effective to prolong the *in vivo* effect of the Type I IFN. It is believed that this language accomplishes that which the examiner has suggested in order to obviate this rejection, particularly in view of the fact that claim 1 is drawn to a method for prolonging the *in vivo* effect of IFN rather than potentiating its effect. Novick '078 and Yeda do not suggest administering a complex. Furthermore, even if it would be obvious to administer IFN and IFNAR separately to the same patient for the reasons suggested by the examiner, it would not be obvious to use an amount of IFNAR effective to prolong the *in vivo* effect of the Type I IFN. Accordingly, claim 1 as a whole and those claims which depend therefrom are non-obvious in light of either or both of Novick

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'078 or the Yeda patent. Reconsideration and withdrawal of this rejection are also respectfully urged.

It is noted that the examiner has acknowledged the allowability of claim 23 if amended to correct the spelling of compliment. As this amendment has now been made, claim 23 should now be in condition for allowance.

It is noted that the examiner has objected to claims 4-6, 12-14 and 18-20 as depending from a rejected base claim, but the examiner has acknowledged that these claims would be allowable if claims 4, 5 and 12 were rewritten in independent form including all the limitations of their respective base claims. However, in view of the fact that the respective base claims have now been amended so as to be made allowable fo the reasons discussed above, there is no reason to rewrite claims 4, 5 and 12 in independent form at the present time.

In view of the indication of allowable subject matter in this case and applicants' good faith attempt to amend the claims in order to claim such allowable subject matter, if the examiner does not feel that the present amendment places the case into condition for allowance, it is requested that the examiner contact the undersigned by telephone in order to work out wording acceptable to both parties in order to appropriately claim the allowable subject matter.

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It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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